AF/#
QAV1644

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 040388/0110

In re Patent Application of
Jean-Francois BACH *et al.*

Serial No. 08/986,568 Group Art Unit: 1644

Filed: December 5, 1997 Examiner: F. VanderVegt

For: METHOD FOR TREATING ESTABLISHED SPONTANEOUS AUTO-IMMUNE DISEASES IN MAMMALS

REQUEST FOR ORAL HEARING

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicant, through their undersigned attorney, hereby request that an oral hearing be scheduled before the U.S. Patent and Trademark Office Board of Appeals in connection with the subject application.

A check in the amount of $260.00 is attached hereto to cover the requisite government fee.

Applicant, therefore, awaits receipt of the Notice of Oral Hearing in due course.

Respectfully Submitted,

10 March 2000
Date

S. A. Bent
Stephen A. Bent
Reg. No. 29,768

Foley & Lardner
3000 K Street, NW
Suite 500
Washington, D.C. 20007-5319

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE HONORABLE BOARD OF PATENT APPEALS AND INTERFERENCES

In re the Application of Bach *et al.*
Application No.: 08/986,568
Filed: December 5, 1997
Docket No.: 040388/0110
For: **METHOD FOR TREATING ESTABLISHED SPONTANEOUS AUTO-IMMUNE DISEASES IN MAMMALS**

REPLY TO EXAMINER'S ANSWER

Appeal from Group 1644

FOLEY & LARDNER
Suite 500
3000 K Street, N.W.
Washington, DC 20007-5109

TABLE OF CONTENTS

I. SUMMARY OF THE ARGUMENT

The examiner's statements reflect a continued misapprehension of the claimed invention and its relationship to the prior art. Rather than rebut the declaration evidence of record, concerning the state of the art at the time of the invention, the examiner propounds a factual conclusion that is clearly erroneous. Hughes *et al.* did not teach that administration of $F(ab')_2$ fragments of an anti-CD3 antibody could induce a durable remission in overt autoimmunity. Similarly, Racadot *et al.* did not suggest anti-CD3 therapy as a means for inducing a durable remission of overt autoimmunity. Accordingly, no combination of prior-art teachings would have led one of ordinary skill in the art to modify the monoclonal antibody of Racadot *et al.*, thereby to reach appellants' claimed invention.

II. ARGUMENT

A. The examiner improperly dismissed the declaration of Dr. Terry Strom by finding, in Hughes et al., a teaching that anti-CD3 $F(ab')_2$ fragment therapy can induce a durable remission in overt autoimmunity

In his declaration of November 15, 1999 ("Strom Declaration"), Dr. Terry Strom attested to several facts that reflect on the state of the art at the time the invention was made, *circa* 1997. From his perspective both as a disinterested party and as a world-renowned expert in the field, Dr. Strom averred that "the knowledgeable reader of Chatenoud *et al.* (1994) would have expected the remission induced by treatment with CD3 antibody to be the result of cytokine-mediation of immune function." Strom Declaration at page 2, first full paragraph. He further noted how it was "well-known [in the relevant time frame] that $F(ab')_2$ fragments are non-mitogenic." *Id.*, second full paragraph. From these observations, Dr. Strom concluded that "a knowledgeable immunologist would have expected that immunotherapy, employing a $F(ab')_2$ fragment of an anti-CD3 antibody, would not trigger cytokine release and, therefore, would not induce a durable, remission of overt autoimmunity." *Id.*

The examiner discounted the Strom declaration out of hand and, yet, did not contest his averments directly. Rather, the examiner simply cited Hughes *et al.* (1994) for the

proposition that non-mitogenic fragments of anti-CD3 antibody induce T-cell hyporesponsiveness *in vivo*. Examiner's Answer page 8, lines 2 to 6. So doing, the examiner has maintained his assertion that the appealed claims are anticipated by Chatenoud *et al.* (1994), as evidenced by Hughes *et al.* (1994). Office Action mailed on January 29, 1999, page 2, lines 15-17.

To justify this assertion, the examiner has had to conclude that Hughes *et al.* taught the capability of anti-CD3 $F(ab')_2$ fragment therapy to induce a durable remission in overt autoimmunity. This conclusion clearly is erroneous as a matter a fact, however.

Hughes *et al.* investigated the effects of anti-CD3 $F(ab')_2$ fragments on autoimmunity, using the murine collagen-induced arthritis model. Briefly, male DBA/1J mice were injected with type II collagen (CII) to induce a chronic, inflammatory polyarthritis involving both cellular and humoral autoimmunity. Concomitant to immunization with CII, the mice were injected with anti-CD3 $F(ab')_2$ fragments to evaluate the therapy's effectiveness on collagen-induced arthritis (CIA). The investigators demonstrated that anti-CD3 $F(ab')_2$ fragment therapy delayed the onset of CIA.

Hughes *et al.* did not even hint that anti-CD3 $F(ab')_2$ fragment therapy might induce a durable remission in overt autoimmunity. As noted above, the Hughes reference merely demonstrated that anti-CD3 $F(ab')_2$ fragment therapy delayed the onset of CIA, when administered concomitantly with CII.

Conversely, Hughes *et al.* said nothing about restoration of self-tolerance. Moreover, there was (and still is) no principle that would allow the skilled artisan to generalize from a delayed onset for CIA to a reasonable expectation of induction of a durable remission in overt autoimmunity. In other words, while a delay in disease onset may be indicative of a therapy's capability to induce unresponsiveness, it has no correlation with effectiveness in inducing a durable remission in overt autoimmunity. For example, prior to the invention, scores of therapies were known to prevent the onset of diabetes in the NOD mouse; however, none had been shown to induce a durable remission in overt disease. See Bowman *et al.*, *Immunology Today* 15:115-120 (1994) (copy appended).

Accordingly, restoration of self-tolerance from overt autoimmune disease can only be assessed using a spontaneous disease model. This point was stressed in the appellants' main brief; for example, see the discussion regarding anti-CD3 $F(ab')_2$ fragment therapy practiced by Chatenoud *et al.* (1994), particularly at page 4, in the fourth paragraph, of the

Brief on Appeal filed November 15, 1999. Like Hughes *et al.*, Chatenoud *et al.* (1994) demonstrated that anti-CD3 $F(ab')_2$ fragment therapy is capable of inducing hyporesponsiveness *in vivo*. That is, Chatenoud *et al.* evaluated anti-CD3 $F(ab')_2$ fragment therapy using a cyclophosphamide-induced diabetes model, and Hughes *et al.* evaluated the therapy using a collagen-induced arthritis model. But both models were incapable of assessing the therapy's durability of unresponsiveness or its effectiveness in inducing a durable remission in overt autoimmunity.

As a matter of fact, therefore, the examiner is wrong to find in Hughes *et al.* a teaching that anti-CD3 $F(ab')_2$ fragment therapy is capable of inducing a durable remission in overt autoimmunity. Indeed, it is incredulous to suggest that Hughes *et al.* in 1994 taught one of reasonable skill in the art that anti-CD3 $F(ab')_2$ fragment therapy is capable of inducing a durable remission in overt autoimmunity, when Dr. Strom, Chief of the Division of Immunology at Beth Israel Deaconess Medical Center and Professor of Medicine at Harvard Medical School, swore that he was not aware of any such therapy in 1997. Accordingly, the rejection under §102(b) should be overruled.

B. Racadot et al. did not teach that anti-CD3 therapy is capable of inducing a durable remission of overt autoimmunity

The examiner has asserted that "it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the effective muromonab-CD3 mAb by humanization as taught by Gussow *et al.* in order to alleviate the anti-murine complications taught by Racadot *et al.*" and to further "modify the humanized muromonab-CD3 by pepsin digestion of the entire humanized antibody to generate $F(ab')_2$ fragments to use for treatment as taught by Chatenoud *et al.* in order to eliminate the massive cytokine release associated with treatment using intact anti-CD3 antibodies." January 29 action at page 5, lines 12-18. The examiner has concluded that "in view of the Chatenoud *et al.* reference's teaching regarding success with non-mitogenic anti-CD3 $F(ab')_2$ fragments, one would have reasonably expected the induction of clonal anergy (nonresponsiveness) seen by Racadot *et al.* (page 202, second paragraph) without the massive detrimental cytokine release associated with intact muromonab-CD3." Examiner's Answer at page 9, lines 6-9.

The examiner errs factually in this regard. Racadot *et al.* did not teach that anti-CD3 therapy is capable of inducing a durable remission of overt autoimmunity. In fact,

Racadot *et al.* stated that "[t]he use of muromonab-CD3 in patients with multiple sclerosis appears to be deleterious, with an exacerbation of clinical symptoms in some patients." See Racadot *et al.*, page 204, 1st column. Besides failing to show that muromonab-CD3 therapy induces a remission in multiple sclerosis, Racadot *et al.* did not discuss the durability of the treatment. Furthermore, the examiner has previously acknowledged that the present invention does not operate *via* the "two-signal" hypothesis of anergy induction. Advisory Action mailed September 20, 1999. Because Racadot *et al.* failed to teach the effectiveness and durability of anti-CD3 therapy, no combination of references would allow one skilled in the art to expect that the success of the present invention could be achieved by modifying the monoclonal antibodies of Racadot *et al.*

The examiner errs in asserting that Racadot *et al.* establishes anti-CD3 treatment as an effective therapy for inducing a durable remission of overt autoimmunity. Accordingly, the appealed rejection under §103 should be overruled.

Respectfully submitted,

10 March 2000
Date

S. A. Bent
Stephen A. Bent
Reg. No. 29,768

Foley & Lardner
3000 K Street, NW
Suite 500
Washington, D.C. 20007-5319